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## Late potentials, ventricular arrhythmias and intervention.

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## Chapter 11

### Summary

Acute myocardial infarction is a very serious disease. In the acute phase, it causes a considerable mortality, and during the subsequent year after discharge another 4-10% of the patients die. Over the last three decades, mortality in the acute phase is decreased (partly due to the introduction of the coronary care unit in hospitals), but unfortunately the mortality in the first year after discharge from the hospital is hardly decreased. This so-called late mortality is caused by recurrent myocardial infarction, congestive heart failure, and ventricular arrhythmias. The latter are the cause of sudden, unexpected death and are the most important cause of this late mortality. Because of the unexpected occurrence of such arrhythmias, much research was performed in order to identify harbingers of these ventricular arrhythmias. The identification of such harbingers is of tremendous importance because it theoretically enables to install preventive treatment in patients with a high risk of sudden death, because, once these arrhythmias occur, treatment is usually too late. One of those harbingers are late potentials that can be detected by means of signal-averaging of the body surface electrocardiogram.

In this thesis the incidence and predictive value of late potentials was studied in various conditions in the pig and in man. Furthermore, the effect of interventions on late potentials was investigated. A review of the recent literature in relation to the studies described in this thesis is presented in Chapter 1.

### Late Potentials as Indicators of a Substrate for Ventricular Arrhythmias

In Chapter 2 a porcine model of ischemia and reperfusion is presented. Late potentials were shown to develop after myocardial infarction, and their relation to inducible ventricular tachycardia was comparable to that in man, but clearly different from that in dogs. Moreover, the absence of collateral coronary circulation makes the porcine heart a feasible model for intervention studies mimicking thrombolysis in man.

The predictive value of late potentials in man for arrhythmic events after myocardial infarction is discussed in Chapter 3. The data corroborate the view that late potentials are harbingers of arrhythmic events. This predictive value is not higher in the presence of QTc prolongation at the twelve lead electrocardiogram. Thus, whereas other investigators reported a higher risk of arrhythmic events when late potentials and a low ejection fraction (< 40%) or complex ventricular arrhythmias are simultaneously present, the results of our study do not indicate that the presence of concomitant QTc prolongation should raise extra concern.

In Chapter 4 we describe a new congenital long QT syndrome, characterized by QTc prolongation at low heart rates. We call this a bradycardia-dependent long QT syndrome, in contrast to the adrenergic-dependent long QT syndromes (such as the Romano-Ward syndrome) in which QTc prolongation is present at high heart rates. In spite of a disconcertingly high incidence of sudden death in this family, previously we never found any clues pointing toward a higher susceptibility to arrhythmias in these subjects. However, a very high incidence of late potentials was found in subjects with the syndrome. Late potentials may be adjuncts in both the detection and in the risk stratification of patients with the syndrome.

The results of the studies described in this section of the thesis show that late potentials are markers of arrhythmic events after myocardial infarction, and that they are also present in other heart diseases. These heart diseases, although rare, become more important in view of the increasing sporting activities in the population with a concomitant increase in sudden death during exercise. The value of late potentials, both for diagnostical purposes and in terms of risk stratification in heart diseases other than myocardial infarction has at present not been studied to a sufficient extent. This issue needs to be addressed in prospective studies.

### **Treatment Strategies that Reduce the Incidence of Late Potentials After Myocardial Infarction**

Angiotensin converting enzyme (ACE) inhibitors are increasingly administered to patients who suffer from an acute myocardial infarction, shortly after the event. Animal studies have shown that the administration of ACE inhibitors during ischemia and reperfusion will render the myocardium less sensitive for ventricular arrhythmias during the first two weeks after the event. Both animal and human data show that (early) administration may also influence the remodeling process of the damaged myocardium, i.e. modulate the substrate development.

The ACE inhibitor perindopril, when administered during ischemia and reperfusion in pigs and during the subsequent days, significantly improved survival. Furthermore, ACE inhibition appeared to prevent the development of late potentials (Chapter 5).

One of the effects of ACE inhibition is enhancement of endogenous bradykinin levels, and in Chapter 6 we showed that bradykinin infusion during ischemia and reperfusion in pigs also prevents the development of late potentials. Therefore, potentiation of endogenous bradykinin partly explains the mechanism of action of ACE inhibition.

Apart from these subchronic effects, ACE inhibition may have an acute effect on inducible or spontaneous ventricular arrhythmias. Similarly, it was shown in Chapter 7 that bradykinin affects the inducibility of ventricular tachycardia. This partly explains the beneficial effect of perindopril as described in Chapter 5.

Another treatment strategy that might reduce the incidence of late potentials after acute myocardial infarction is pharmacological reperfusion. Thrombolysis-induced

patency of the infarct-related artery is a prerequisite for the treatment of late potentials. Late potentials are considered to be harbingers of life-threatening ventricular arrhythmias. Thrombolysis has been shown to reduce the incidence of late potentials and of arrhythmic events. Larger studies are needed to confirm these findings. Other studies are ongoing.

The results of the present study show that late potentials were the reason for the arrhythmic events. The preliminary results of the present study show that late potentials are harbingers of life-threatening ventricular arrhythmias. However, the trend toward a reduction in the incidence of late potentials after thrombolysis is not statistically significant. Further experiments (Chapter 8) are needed to confirm these findings. The value of late potentials for risk stratification in heart diseases other than myocardial infarction has at present not been studied to a sufficient extent. This issue needs to be addressed in prospective studies.

The present study shows that late potentials are markers of arrhythmic events after myocardial infarction, and that they are also present in other heart diseases. These heart diseases, although rare, become more important in view of the increasing sporting activities in the population with a concomitant increase in sudden death during exercise. The value of late potentials, both for diagnostical purposes and in terms of risk stratification in heart diseases other than myocardial infarction has at present not been studied to a sufficient extent. This issue needs to be addressed in prospective studies.

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## Late Potentials

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patency of the infarct related artery appears to be the mechanism by which the develop-  
ment of late potentials is prevented. Although Chapter 3 showed that late potentials are  
harbingers of life-threatening arrhythmic events, and although streptokinase-induced  
thrombolysis reduced the incidence of late potentials (Chapter 8), it could not be  
shown that reduction of late potentials is paralleled by a significant reduction in ar-  
rhythmic events during long-term follow-up. Similar results were reported by others.  
Larger studies with sufficient power to detect differences as suggested by our and  
other studies are needed.

The results of previous studies and those described in the Chapters 5 and 6  
were the reason to perform the Captopril And Thrombolysis Study (Chapter 9). The  
preliminary results of this study do not yet allow to draw definite conclusions. How-  
ever, the trend apparently induced by captopril treatment during the early phase of  
thrombolysis is favorable and fully in agreement with the observations in animal ex-  
periments (Chapters 5 and 6). Therefore we feel that further research in the field  
of late potential development after myocardial infarction and its modification due to  
thrombolytic therapy and ACE inhibitors is urgently required.

The present thesis shows that late potentials are markers of arrhythmic events  
after myocardial infarction and that the development of late potentials can indeed be  
influenced by interventions in the early stage of acute myocardial infarction. Further  
research is mandatory and should focus on the clinical relevance of the lowered  
incidence of late potentials after intervention.

Questa tesi tratta l'incidenza e il valore prognostico dei potenziali tardivi in varie  
situazioni del miocardio e nell'uomo. Inoltre, è analizzato l'effetto dei trattamenti sui  
potenziali tardivi. Una rassegna della letteratura recente in relazione con gli studi  
presentati in questa tesi si trova nel Capitolo 1.

## Potenziali tardivi come indicatori delle condizioni della generazione di aritmie ventricolari

Il Capitolo 2 tratta lo studio dell'ischemia e la ripercussione cardiaca su un modello  
animale. I potenziali tardivi si formano dopo l'infarto miocardico. La relazione tra  
potenziali tardivi e la tachicardia ventricolare indotta da stimolazione ventricolare  
programmata, era simile a quella nell'uomo, però chiaramente diversa da quella nel  
cane. Inoltre, data la mancanza di una correlazione costante collimata nel corso  
del miocardio, questo modello è appropriato per lo studio di interventi che alterano la  
aritmia nell'uomo.

Il Capitolo 3 tratta il significato prognostico dei potenziali tardivi nell'uomo  
per eventi aritmici dopo l'infarto miocardico. I risultati confermano che i potenziali  
tardivi sono i precursori degli eventi aritmici. Il significato prognostico non è aumentato  
quando c'è allungamento simultaneo dell'intervallo QTc sull'elettrocardiogramma.  
Dunque, anche se il rischio di eventi aritmici aumenterebbe quando i potenziali tar-  
divi e una frazione di ricorrenza < 40% o aritmie ventricolari vengono non si